PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erik H.F. Wong et al.

Serial No.: 10/758,864

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Title: METHOD OF TREATING PERIPHERAL NEUROPATHY

Group Art Unit: 1614

Examiner: Phyllis G. Spivack

Attorney Docket No.: 30744/6248.11

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on **August 7, 2006.**

Sandip H. Patel (Reg. No. 43,848)
Attorney for Applicants

RESPONSE TO FINAL OFFICIAL ACTION

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This paper is being presented in response to the final official action dated April 6, 2006, wherein all of the pending claims (i.e., claims 1-12, 14-17, 39, 40, and 54-67) have been rejected under 35 USC § 112, ¶ 1, as allegedly lacking an enabling disclosure. The final action also newly rejects the pending claims under the judicially-created doctrine of obviousness-type double patenting over claims 1-32 of U.S. Patent No. 6,465,458. Reconsideration and withdrawal of the rejections are respectfully requested in view of the following remarks.

This paper is timely filed as it is accompanied by a petition under 37 CFR § 1.136(a) for a one-month extension of time to file a response to the outstanding action, a request for continued examination under 37 CFR § 1.114, and payment of the associated petition and request fees. This paper also is accompanied by a terminal disclaimer pursuant to 37 CFR § 1.321(c), and payment of the fee associated therewith.

The applicants hereby acknowledge with appreciation the courteous interview granted by the examiner on June 26, 2006, to the applicants' representatives (Sandip H. Patel, Keith S. Ruddock, and Malcolm J. Stoker, Ph.D.). The applicants also acknowledge receipt of the examiner's "Interview Summary," dated June 27, 2006. Contrary to the

indication in that summary, no agreement with respect to the pending claims was reached during that interview.

A complete listing of the existing claims is not required (or presented herein) because no changes are being made to the claims, no claims are being canceled, and no claims are being added. *See* 37 CFR § 1.121(c).

On February 7, 2006, the applicants submitted an information disclosure statement (including a Form PTO-1449 and the publications identified therein) pursuant to 37 CFR §§ 1.56 and 1.97(c)(2). The Public PAIR portal of the U.S. Patent and Trademark Office's website indicates that the Patent Office received the IDS on February 10, 2006. The final action, however, does not acknowledge the IDS and did not include an examiner-initialed copy of the Form PTO-1449. The applicants request consideration of the IDS and the information contained therein in the next official action on the merits.

I. The 35 USC § 112, ¶ 1, Rejection is Traversed

The pending claims are directed to methods of treating an individual suffering from peripheral neuropathy. The methods generally include administration of a therapeutic amount of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. Embodiments of these methods can diminish adverse side effects.

The first action enumerated the various *Wands* factors that the Patent Office considered in determining the applicants' compliance with the § 112, ¶ 1, enablement standard. The applicants addressed each of those *Wands* factors in responding to the first action. The final official action, identifies only one of the *Wands* factors—the breadth of the claims—in supporting the enablement rejection. The applicants take the Patent Office's silence with respect to the other *Wands* factors in the final action as its conciliation that the applicants' arguments regarding those factors in response to the first action were persuasive. *See* 37 CFR § 1.113(b) (stating that in making a final rejection, "the examiner shall repeat or state all grounds of rejection then considered applicable to the claims in the application, clearly stating the reasons in support thereof").

The final action acknowledges the claimed invention and the declarations of Drs. Arneric and Ratcliffe, states that peripheral neuropathy is "broadly considered to be diseases of the peripheral nervous system that are characterized by inflammation, pain, paralysis and/or muscle wasting," and states that "peripheral neuropathy results from genetic or idiopathic disorders, viral or microbial diseases other than herpes, as hepatitis, mononucleosis or diphtheria; porphyric, toxic or organic substance-induced, such as carbon monoxide; metal-induced, as arsenic, mercury, lead or antimony; or carcinoma." Action at pp. 2-3. The action concludes that "[t]here is no support for treating peripheral neuropathy and, optionally, diminishing adverse side effects." *Id.* at 2. The action further concludes that the

pending claims "are drawn to subject matter that is far broader than the patient population having post-herpetic neuralgia." *Id.* at 3.

The rejection is strongly traversed as the final action (like the first action) does not establish a *prima facie* case that the claims are not enabled. The rejection is additionally traversed in view of additional evidence supplied herein.

A response to the outstanding § 112, ¶ 1, rejection is set forth below.

A. Proper Basis for a § 112, ¶ 1, Lack of Enablement Rejection

For the sake of brevity, the full description of the proper basis for a § 112, ¶ 1, lack of enablement rejection, set forth in the response filed January 17, 2006, is incorporated herein by reference.

The breadth of the claims is merely one of the various *Wands* factors that the Patent Office must consider when determining whether there is sufficient evidence to support a conclusion that a patent application satisfies (or does not satisfy) the enablement requirement, and whether any necessary experimentation is "undue." *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The Patent Office, however, may not conclude that a patent application is not enabling based on an analysis of only one of those factors—e.g., the breadth of the claims—while ignoring one or more of the other factors; instead, a conclusion of non-enablement must be based on the evidence as a whole. *See id.* at 740.

A disclosure teaching how to make and use an invention in terms corresponding in scope to those defining the claimed subject matter complies with the enablement requirement (in § 112, ¶ 1), *unless* there is a reason to doubt the objective truth of the disclosure relied upon for enabling support. *See In re Marzocchi*, 439 F.2d 220, 223-24 (CCPA 1971). In determining (and reconsidering) whether the patent application includes an enabling disclosure of the claimed invention, the Patent Office must consider all evidence in the record, weighing evidence that confirms enablement against evidence that refutes enablement. *See In re Wands*, 858 F.2d at 737, 740.

B. Analysis of the "Breadth of the Claimed Invention" *Wands* Factor

1. The Claimed Invention

The claimed invention relates to methods of treating an individual suffering from peripheral neuropathy. These methods include administering a therapeutically effective amount of optically pure (S,S) reboxetine (or a pharmaceutically acceptable salt thereof) to the individual. *See, e.g.*, claim 1. Embodiments of these methods can diminish adverse side effects, when, for example, a total dose of about 0.1 to about 10 mg/day of optically pure (S,S) reboxetine (or a pharmaceutically acceptable salt thereof) is administered to the individual. *See, e.g.*, claim 39.

2. The Patent Office's Position as Set Forth in the Final Action

The final action states that the peripheral neuropathy is "broadly considered to be diseases of the peripheral nervous system that are characterized by inflammation, pain, paralysis and/or muscle wasting." Action at p. 2. The final action also states that "peripheral neuropathy results from genetic or idiopathic disorders, viral or microbial diseases other than herpes, as hepatitis, mononucleosis or diphtheria; porphyric, toxic or organic substance-induced, such as carbon monoxide; metal-induced, as arsenic, mercury, lead or antimony; or carcinoma." Action at p. 3 (citing Harrison's Principles of Internal Medicine, 1806 (Table 331) (8th ed., 1977)). These observations (whether or not true) do not affect the breadth a skilled artisan would attribute to the claimed invention such that this *Wands* factor—the breadth of the claimed invention—should weigh against enablement. This skilled artisan readily understood the meets and bounds of the term "peripheral neuropathy" and how peripheral neuropathy may be treated. Based on this understanding, the skilled artisan would have absolutely no reason to doubt the objective truth of the teachings set forth in the application that the claimed methods could treat peripheral neuropathy.

3. The Level of Ordinary Skill in the Art

The level of skill in the art is generally that of a Ph.D. or M.D. with expertise in the area of neurology, and an example of a Ph.D. with expertise in the area of neurology is a person having a Ph.D. in pharmacology and experience in the neurosciences. Attached hereto as Appendix "A" is a "Declaration of Dr. Malcolm John Stoker Pursuant to 37 CFR § 1.132," dated July 31, 2006. Dr. Stoker has reviewed the final action and this patent application, and he is familiar with the subject matter disclosed therein. *See* Stoker Declaration at ¶s 1-2. Dr. Stoker's education, which includes advanced degrees in pharmacology, and professional experiences, which include Clinical Research Manager or Director positions at numerous pharmaceutical companies and his position as a Senior Director in the Neuroscience and Pain therapeutic areas at Pfizer Limited (also referred to herein as "Pfizer"), qualify him to comment on the subject matter of the application. *See* Stoker Declaration at ¶s 3-6.

4. Diagnosing Peripheral Neuropathy

The peripheral nervous system consists of motor and sensory nerves that connect the brain and spinal cord (i.e., the central nervous system) to every other part of the body—i.e., it consists of the nerves outside of the central nervous system. Stoker Declaration at ¶ 7(a). "Peripheral neuropathy" is a term that describes a disorder of, or damage to, the peripheral nervous system. The disorder or damage may affect a single nerve (mononeuropathy) or one or more nerves simultaneously (polyneuropathy). *See generally*, The Merck Manual of Diagnosis and Therapy, 16th ed., p. 1518 (Merck Research Labs., Rahway, NJ, 1992) (copy attached to the Stoker Declaration as Exhibit "A"). Stoker

Declaration at ¶ 7(b). Although a variety of events may cause damage to the peripheral nervous system, these events generally produce **common symptoms** indicative of peripheral neuropathy. These symptoms include, for example, pain, weakness, sensory loss, and tingling sensations. *See generally*, The Merck Manual at p. 1518 (copy attached to the Stoker Declaration as Exhibit "A"). Consequently, and as set forth in The Merck Manual (at p. 1520), peripheral neuropathy is art-recognized and diagnosed as "a symptom complex rather than a disease entity." Stoker Declaration at ¶ 7(c). Moreover, and in contrast to the unsupported assertion in the final action (p. 2), peripheral neuropathy is **not** considered to be a disease of the peripheral nervous system; instead, peripheral neuropathy is art-recognized as a disorder of the peripheral nervous system characterized by a complex of common symptoms.

The skilled artisan recognizes that treatment of a symptom complex, such as peripheral neuropathy, may be accomplished by alleviating or otherwise controlling one or more symptoms. This treatment is consistent with the teachings in the specification, which state, for example:

> Treatment or prevention of above disorders involves the administration of reboxetine in a manner and form that result in a reduction in the symptoms of the disease or disorder.

Specification at p. 29, lines 12-14. Although the foregoing statement from the specification refers to treatment with (racemic) reboxetine, the skilled artisan, having considered the application's teachings as a whole, would have readily understood that the statement is applicable to treatments with (S,S) reboxetine as well. Stoker Declaration at ¶ 7(d).

Individual peripheral neuropathies are diagnosed by recognition of a distinguishing set of symptoms. Peripheral neuropathy caused by diabetes is the most common form and is generally referred to as diabetic peripheral neuropathy (DPN). DPN is a representative polyneuropathy pain model. Post herpetic neuralgia (PHN) is another peripheral neuropathy and classically presents after a patient has suffered a Herpes Zoster infection. PHN is a representative mononeuropathy pain model. PHN is easily diagnosed because it has a symptom profile that includes many of the common symptoms indicative of peripheral neuropathy, including pain. This symptom profile makes PHN useful for clinical study of painful peripheral neuropathies, and also qualifies PHN as a representative disorder to study when considering the effective treatment of painful peripheral neuropathies. Both PHN and DPN are well-known neuropathic pain syndromes. *See* Stoker Declaration at ¶ 8.

5. Prior Treatments for Peripheral Neuropathy

The first official action stated that the prior art "does not presently recognize methods of preventing peripheral neuropathy" and that "this particular art is immature." There is absolutely no support for such statements. The successor-in-interest (Pfizer.) to the assignee

(Pharmacia & Upjohn Company) of the current application commercially manufactures, with approval from the European Medicines Evaluation Agency (EMEA, London), pregabalin[1] capsules for the treatment of peripheral neuropathic pain in adults, and sells those capsules throughout the European Union under the product name "LYRICA®." Stoker Declaration at ¶ 9.

In bringing the LYRICA® product to market, Pfizer (and Warner-Lambert Company, which Pfizer acquired in 2000) demonstrated through a program of clinical studies that pregabalin is safe and effective in treating patients suffering from PHN and in treating patients suffering from DPN. *See* European Summary of Product Characteristics (SPC) for the LYRICA® product at § 5.1 at p. 11 (copy attached to the Stoker Declaration as Exhibit "B").[2] Based on results Pfizer obtained through this program, the EMEA provided Pfizer with its approval to sell the LYRICA® product throughout the European Union for the treatment of peripheral neuropathic pain—not simply the treatment of PHN and DPN. Consequently, this agency has recognized that demonstrated efficacy in treating patients suffering from PHN and demonstrated efficacy in treating patients suffering from DPN are indicative of efficacy in treating patients suffering from pain associated with peripheral neuropathy.[3] Stoker Declaration at ¶ 10.

The program of clinical studies Warner-Lambert Company (which Pfizer acquired in 2000) undertook to obtain approval of the LYRICA® product—i.e., beginning clinical studies in 1998 with patients suffering from PHN or DPN—is consistent with a program a pharmaceutical company would undertake in seeking to obtain approval of a product for the treatment of peripheral neuropathies because PHN is useful for clinical study of painful peripheral neuropathies, and its symptom profile qualifies PHN as a representative disorder to study when considering the effective treatment of painful peripheral neuropathies. Moreover, both PHN and DPN are well-known neuropathic pain syndromes. Stoker Declaration at ¶ 11.

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[1] Pregabalin is the *S* enantiomer of 3-(aminoethyl)-5-methylhexanoic acid. Pregabalin is an anticonvulsant that is structurally and pharmacologically related to gabapentin. Gabapentin has been approved in many European member states for the treatment of neuropathic pain, and is commercially available under the product name "NEURONTIN®."

[2] According to this SPC, "[p]regabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin." See Exhibit B (attached to the Stoker Declaration) at p. 11 (§ 5.1).

[3] Additional clinical studies with the LYRICA® product are on-going relative to other peripheral neuropathies, such as, for example, neuropathic pain induced by multiple sclerosis (Exhibit "C" attached to the Stoker Declaration), neuropathic pain subsequent to trauma (Exhibit "D" attached to the Stoker Declaration), neuropathic pain induced by HIV (Exhibit "E" attached to the Stoker Declaration), and neuropathic pain associated with lumbo-sacral radiculopathy (Exhibit "F" attached to the Stoker Declaration).

6. Clinical Studies Treating Peripheral Neuropathy With (S,S) Reboxetine

Dr. Stoker reviewed a copy of, and is familiar with the subject matter described in the September 23, 2005, declaration of Dr. Sian Louise Ratcliffe, which was submitted to the Patent Office in response to the first official action in this application. Dr. Ratcliffe is a colleague of Dr. Stoker and they are commonly-employed by Pfizer. The subject matter of Dr. Ratcliffe's declaration relates to an analysis of certain results obtained in a clinical study (namely, Pfizer Study Protocol A6061001) performed by Pfizer. *See generally*, Stoker Declaration at ¶ 12.

Pfizer studied (S,S) reboxetine (in Pfizer Study Protocol A6061001) in a five-week randomized, double-blind, placebo-controlled, multi-center study with patients (also referred to as "subjects") suffering from PHN who were gabapentin treatment failures:

> (a) Fifty-two centers in the United States enrolled subjects into the study.
>
> (b) Those subjects showing no or minimal improvement on the Patient Global Impression of Change (PGIC) after treatment with gabapentin (1800 mg/day), or who were unable to tolerate gabapentin (1800 mg/day) were randomized to receive a placebo or (S,S) reboxetine for a period of five weeks.
>
> (c) The randomization was stratified by age into those aged less than 75 years (non-elderly) and those aged 75 years or more (elderly).
>
> (d) Those subjects receiving (S,S) reboxetine received (S,S) reboxetine doses that escalated over a two-week period to a maximum of 6 mg/day for non-elderly subjects, and to a maximum of 4 mg/day for elderly subjects.
>
> (e) A total of 206 subjects were randomized to treatment and are included in an intent-to-treat (ITT) population. A total of 146 subjects were correctly randomized, adhered closely to the protocol treatment regimen, completed baseline and week-5 assessments and, therefore, are included in the per protocol (PP) population. The primary population for analysis is the ITT population.
>
> (f) Baseline patient characteristics of the subjects were similar across treatment groups. For example, approximately 88% of the subjects were white, 48% were female, and the mean age of the subjects was 68.5 years. Sixty-seven percent of patients who were randomized subsequent to the gabapentin treatment phase fulfilled criteria for therapeutic failure with gabapentin, while the remaining 33% had failed to tolerate gabapentin (1800 mg/day).

Stoker Declaration at ¶ 13.

According to Dr. Stoker, the results of the study protocol described in Dr. Ratcliffe's declaration demonstrate that (S,S) reboxetine is effective to treat pain associated with PHN (a peripheral neuropathy). *See, e.g.*, the Ratcliffe declaration at p. 12 (Appendix 5) (stating that "ssRBX [(S,S) reboxetine] was clearly efficacious in the treatment of PHN in subjects who are GBP [gabapentin] treatment failures"). Stoker Declaration at ¶ 14. The record, thus, already contains evidence of a clear nexus between a method of treating PHN and the efficacy data and conclusions set forth in Dr. Ratcliffe's declaration.

Dr. Stoker further declares that additional results of the study protocol also demonstrate this efficacy:

> (a) According to an ITT population Last Observation Carry Forward (LOCF) analysis, the difference in the adjusted mean change (from baseline to week five) in weekly average pain score between (S,S) reboxetine and the placebo (i.e., (S,S) reboxetine minus placebo) was –0.82 (P <0.001) with a corresponding 90% confidence interval (90% CI) of -1.24, -0.41. For the per protocol analysis, the difference in adjusted mean changes was -1.15 (90% CI: -1.63, -0.67).
>
> (b) The (S,S) reboxetine-placebo difference for pain diary data was highly and statistically significant across both ITT-LOCF and per-protocol data-sets. The point estimates of the (S,S) reboxetine-placebo difference were -0.82 (ITT-LOCF) and -1.15 (per protocol). This study was powered for a delta of -1.0 to accommodate the treatment-resistant nature of the study population.
>
> (c) The robustness of these results is underscored by the results obtained for the secondary outcome measure, including responder rates and PGIC, which support those obtained for the primary outcome measure. The foregoing results from Pfizer Study Protocol A6061001 are evidence that (S,S) reboxetine is effective to treat PHN, a peripheral neuropathy, in patients who have failed to respond to an adequate course of treatment with gabapentin.

Stoker Declaration at ¶ 15. Dr. Stoker, thus, further reinforces the record evidence of a nexus between the a method of treating PHN and the efficacy data obtained in the completed clinical studies.

On the basis of the favorable efficacy and adverse events results Pfizer obtained in Pfizer Study Protocol A6061001, Pfizer has initiated a clinical study in patients suffering from pain associated with DPN. Stoker Declaration at ¶ 16. These additional clinical studies are entirely consistent with the program of studies a pharmaceutical company would undertake in seeking to obtain approval of a product for the treatment of peripheral neuropathies, and it is reasonable to conclude that (S,S) reboxetine would be effective in the general treatment of painful peripheral neuropathy for at least the following reasons:

> (a) PHN is easily diagnosed because it has a symptom profile that includes many of the common symptoms indicative of peripheral neuropathy, including pain. This symptom profile makes PHN useful for clinical study of painful peripheral neuropathies, and also qualifies PHN as a representative disorder to study when considering the effective treatment of painful peripheral neuropathies. *See* ¶ 8(c) [of the Stoker Declaration].
>
> (b) The results of Pfizer Study Protocol A6061001 substantiate the efficacy of (S,S) reboxetine in the treatment of PHN, a peripheral neuropathy.
>
> (c) A regulatory authority (namely the EMEA) has recognized that demonstrated efficacy in treating patients suffering from PHN and demonstrated efficacy in treating patients suffering from DPN are indicative of efficacy in treating patients suffering from pain associated with peripheral neuropathy. *See* ¶ 10 [of the Stoker Declaration].

Stoker Declaration at ¶ 17.

C. The § 112, ¶ 1, Non-Enablement Rejection Is Traversed

The Patent Office's final action (like its first action) does not provide a "reasonable" basis to question the enablement the patent application provides for the claimed invention. *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (stating that the Patent Office must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). For example, the final action asserts that peripheral neuropathy is a disease of the peripheral nervous system, but identifies no evidence supporting this assertion. The final action also concludes that that the application fails to enable the claimed invention simply because the Patent Office (mistakenly) believes that the claimed invention is broader than the disclosure and the knowledge base of the skilled artisan. The final action, however, cites to no authority for the proposition that it may reach this conclusion while ignoring all of the other evidence (as applied to other *Wands* factors) that compels a conclusion that the claimed invention is enabled. The Patent Office **must** identify evidence and legal authority supporting its factual allegations and legal conclusions that the claimed invention is not adequately supported by the patent application:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [i.e., non-enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In re Marzocchi, 439 F.2d at 223-24. Without such evidence and authority, the Patent Office cannot set forth a "reasonable" basis for questioning the enablement.

Even if one were to conclude that the action provides a "reasonable" explanation questioning enablement, an analysis of **all** of the *Wands* factors considering the evidence as a whole compels a conclusion that the patent application describes the claimed invention in compliance with § 112, ¶ 1. Furthermore, and in view of the post-application filing evidence of selectivity (Arneric declaration), diminished adverse side effects (Ratcliffe declaration), and efficacy (Ratcliffe and Stoker declarations), the applicants respectfully, but strongly, traverse the § 112, ¶ 1, non-enablement rejection.

The non-enablement rejection set forth at pages 2 and 3 of the final action is premised merely on the Patent Office's (mistaken) belief that the claimed invention is broader than the disclosure and the knowledge base of the skilled artisan. Not only is that belief mistaken, but the breadth of the claims is only one of the various *Wands* factors that the Patent Office must consider when determining whether there is sufficient evidence to support a conclusion that a patent application satisfies (or does not satisfy) the enablement requirement, and whether any necessary experimentation is "undue." *See In re Wands*, 858 F.2d at 737. Consideration and analysis of the *Wands* factor relating to the breadth of the claimed invention lead to a finding that the breadth is not fatally expansive as suggested in the action. Even if, however, an opposite finding could be reached, it would still be improper for the Patent Office to premise its conclusion of non-enablement solely on this finding, while ignoring one or more of the other factors; instead, a conclusion of non-enablement must be based on the evidence as a whole. *See id.* at 740.

A person skilled in the art to which the invention is most nearly connected to make and use the claimed invention includes, according to the action, a person having a Ph.D. with expertise in the area of neurology, which, according to the applicants, would include a person having a Ph.D. in pharmacology and experience in the neurosciences.

As argued in the response to the first official action, the specification describes **how to make** optically pure (S,S) reboxetine (and a composition containing the same and/or a pharmaceutically acceptable salt thereof) used in the recited treatment methods at, for example, page 22, line 1, to page 24, line 11. Furthermore, the specification describes **how to practice** the claimed methods by specifying desirable and preferable daily doses at, for example, page 24, line 12, to page 25, line 3. The specification further states, at p. 25, line 29, to p. 26, line 2, that "the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient." Still further, the specification teaches the skilled artisan that peripheral neuropathy

can be treated by administering (S,S) reboxetine in a manner and form that results in a reduction in the symptoms of peripheral neuropathy. *See* Stoker Declaration at ¶ 7(d). This teaching is entirely consistent with the art's recognition that peripheral neuropathy is a symptom complex and not a disease entity. *See* Stoker Declaration at ¶ 7(c) (quoting The Merck Manual at p. 1520).

Indeed, the declarations of Drs. Ratcliffe and Stoker overwhelmingly support a finding that the claimed methods are effective in treating peripheral neuropathy (a symptom complex). Specifically, Dr. Stoker's declaration provides, *inter alia*, evidence that a person having a Ph.D. in pharmacology and experience in the neurosciences understood that: (a) "peripheral neuropathy" is a term that describes a disorder of, or damage to, the peripheral nervous system; (b) although a variety of events may cause damage to the peripheral nervous system, these events generally produce **common symptoms** indicative of peripheral neuropathy; (c) treatment of a symptom complex, such as peripheral neuropathy, may be accomplished by alleviating or otherwise controlling one or more symptoms; and, (d) demonstrated efficacy in treating patients suffering from PHN and demonstrated efficacy in treating patients suffering from DPN are indicative of efficacy in treating patients suffering from pain associated with peripheral neuropathy. *See* Stoker Declaration at ¶s 7 and 17.

Having described how to make the composition recited in the claimed methods and how to practice these methods, the specification also describes numerous advantages the invention provides over certain prior art such as, for example, reduced dosages and reduced adverse side effects. Specification at p. 11, line 28, to p. 12, line 13. The specification, thus, describes the breadth of the claimed invention, specifically teaching administration of (S,S) reboxetine in a manner and form that results in the reduction of the symptoms of peripheral neuropathy, identifying a substantial reduction in the customary daily dosage of commercially-available racemic reboxetine when using an optically pure (S,S) reboxetine, and teaching that the claimed treatment methods may result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine.

The claimed invention is based on the applicants' finding (and substantiation) that (S,S) reboxetine is a highly selective noradrenaline (norepinephrine) reuptake inhibitor, which is devoid of effects on other neurotransmitters. *See* the Stoker Declaration at ¶ 18. The successor-in-interest to the assignee of this application—i.e., Pfizer—has demonstrated that (S,S) reboxetine is effective in treating PHN, a peripheral neuropathy. *See* Section I.B.6, above. The knowledge base in the prior art relative to Pfizer's clinical studies to bring its LYRICA® product to market, includes the known efficacy of anticonvulsants (e.g., pregabalin) in treating painful peripheral neuropathies. *See* Section I.B.5, above. This knowledge base, coupled with the applicants' findings and Pfizer's demonstration of efficacy may be

considered as strong support for the conclusion that that (S,S) reboxetine would have a reasonable likelihood of success in treating painful peripheral neuropathy. *See* the Stoker Declaration at ¶ 19. A person having a Ph.D. in pharmacology and experience in the neurosciences would **not** consider the teachings in the application as incredible or otherwise non-enabling relative to the breadth of the invention recited in the pending claims.

The absence of efficacy data in the application neither detracts from this conclusion nor does it support a conclusion that that the application is not enabling. A salient purpose of the patent laws is to encourage prompt disclosure of inventions. A requirement that this application should have included efficacy data would have discouraged the applicants from promptly disclosing and teaching their discovery for the public's benefit until such data were available, in contravention to the guiding principles underlying § 112. *See* MPEP § 2164.02 (8th ed. Rev. 3, Aug. 2005) (stating that compliance with the enablement requirement does not turn on whether the patent application discloses a working example).

Based on an analysis of **all** of the *Wands* factors (as set forth in the response to the first action) and consideration of the evidence as a whole, it is respectfully submitted that the patent application includes a description of the claimed invention in compliance with § 112, ¶ 1, such that the rejection, upon reconsideration, should be withdrawn. In reconsidering whether the patent application includes an enabling disclosure of the claimed invention, the Patent Office must consider all evidence in the record, weighing evidence that confirms enablement against evidence that refutes enablement. *See In re Wands*, 858 F.2d at 737, 740. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. The Obviousness-Type Double Patenting Rejection

The pending claims have been rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-32 of U.S. Patent No. 6,465,458. The entirety of the basis for the rejection is as follows:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because according to the Ratcliffe Declaration, the patient population having post-herpetic neuralgia, an example of peripheral neuropathy, experienced chronic neuropathic pain.

See p. 4 of the action. The rejection is traversed and/or moot, and reconsideration and withdrawal of the rejection are respectfully requested in view of the response provided below.

A. Proper Basis for an Obviousness-Type Double Patenting Rejection

Congress limits the duration of a patentee's right to exclude others from practicing a claimed invention to a statutorily-prescribed term. 35 USC § 154(a)(2). Non-statutory, or "obviousness-type," double patenting is a doctrine judicially created to prevent claims in

separate patent applications or patents from issuing where those claims do not recite the "same" invention, but nonetheless claim inventions so alike that granting both inventions exclusive rights would effectively extend patent protection beyond the statutorily-prescribed term. *See generally, Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001); *see also Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 686 (Fed. Cir. 1990); *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985) (explaining that, even though no explicit statutory basis exists for obviousness-type double patenting, the doctrine is necessary to prevent a patent term extension through claims in a second patent that are patentably indistinct from those in the first patent).

An obviousness-type double patenting analysis is "analogous to [a failure to meet] the nonobviousness requirement of 35 USC § 103" except that the specification of the patent principally underlying the double patenting rejection cannot be considered prior art. *See* MPEP §804(II)(B)(1) (8th ed., rev. 3, Aug. 2005); *see also, General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279 (Fed. Cir. 1992) (stating that the disclosure of the patent principally underlying the rejection may not be used as prior art). During prosecution, therefore, the Patent Office bears the burden of establishing a *prima facie* case that the application claims are obvious over the claims in a commonly-assigned patent. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988) (stating that the PTO "has the burden under § 103 to establish a *prima facie* case of obviousness"). The PTO's conclusion of obviousness-type double patenting must be made in light of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Generally, an obviousness-type double patenting rejection should make clear: (a) the differences between the inventions defined by the conflicting claims; and, (b) reasons why a person having ordinary skill in the art would conclude the invention recited in the application claims would have been an obvious variation of (i.e., patentably indistinct from) the invention recited in the earlier patent claims. *See generally*, MPEP § 804(II)(B)(1); *see also, Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326-27 (Fed. Cir. 1999). An application claim is patentably indistinct from an earlier patent claim if the application claim is obvious over (or anticipated by) the earlier patent claim. *In re Longi*, 759 F.2d at 896 (affirming a holding of obviousness-type double patenting because the claims at issue were obvious over claims in four prior art patents); *In re Berg*, 140 F.3d 1428, 1437 (Fed. Cir. 1998) (affirming a holding of obviousness-type double patenting where a patent application claim to a genus is anticipated by a patent claim to a species within that genus).

B. The Obviousness-Type Double Patenting Rejection Is Traversed and/or Moot

The action does not set forth a *prima facie* case demonstrating that claims 1-32 of the '458 patent either anticipate or render obvious the pending claims in this application.